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Paraneoplastic leukemoid reaction as a marker of tumor progression in non-small cell lung cancer

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Abstract
Background: Paraneoplastic leukemoid reaction (PLR) is a well-described entity in which the white blood cell count expands to greater than 50,000/mm^3 in association with malignancy. It is thought to occur in approximately 10–15% of cancers. Notably, PLR is known to be predictive of a poor prognosis. Recent work has demonstrated that there may be a relationship between PLR activated by intratumoral production of granulocyte colony-simulating factor (G-CSF), the RAS/RAF/MEK pathway and tumorogenesis. Specifically, activation of the RAS/RAF/MEK pathway is thought to regulate G-CSF production, which in turn, mediates expansion and mobilization of cells that produce factors that promote tumor metastasis.
Methods/results: In this report we demonstrate the PLR response to treatment in a patient with non-small cell lung cancer. Additionally, we demonstrate elevated G-CSF in the patient's serum 507 pg/ml (0–39.1 pg/ml) and positive staining by immunohistochemistry of G-CSF in the patient's tumor tissue. Finally, we describe a possible pathway by which this promotes tumor spread.
Conclusion: Though G-CSF has been traditionally viewed as a prognostic marker, here we provide evidence that it may be a valuable marker to investigate for treatment response at a cellular level.

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1. Introduction

The presence of leukocytosis associated with solid tumors has been documented for many decades [1]. The first demonstration that it was the tumor itself producing a colony-stimulating agent came in 1977 when Asano et al. demonstrated that serial transplantation of human lung cancer tissue from a patient with neutrophilia into mice caused neutrophilia in recipient mice as well [2]. The formal definition of a leukemoid reaction is a white blood cell (WBC) count $>50{,}000/mm^3$ with a predominance of neutrophil precursors. When this elevation in the WBC count is associated with malignancy it is termed a paraneoplastic leukemoid reaction (PLR) [3]. The differential diagnosis of leukemoid reaction includes infection, hematologic malignancy, iatrogenic origin (e.g. steroids, growth factors), solid tumor spread to bone and PLR. Two different case series have reviewed the frequency of PLR. Granger et al. evaluated 3770 consecutive solid tumor patients and found that, of the 758 patients with extreme leukocytosis, 77 (10%) of these patients had PLR. Interestingly, only 13 of the 77 patients (17%) had non-small cell lung cancer (NSCLC), but 41 (53%) patients overall had tumors involving the lungs [4]. Kasuga et al. evaluated a series of 227 patients with lung carcinoma and identified 33 (14.5%) patients with PLR. They also found that 16 patients showed elevated serum granulocyte colony-simulating factor (G-CSF) levels with 12 tumors staining positive for G-CSF by immunohistochemisty (IHC) [5]. Another notable finding of the elevated WBC count in these case series and other case reports is that leukemoid reactions are predictive of a poor prognosis. In a study by Granger et al., 76% of patients diagnosed with PLR died within 12 weeks. Other series and case reports have noted similar prognostic information [5,3].

Here we report the first description, to our knowledge, of non-small cell adenocarcinoma of the lung that evolved during treatment to have a PLR that was responsive to both systemic treatment and radiation therapy.

2. Case history

A 51-year-old man initially presented with a protracted period of cough, night sweats, recurrent fevers and weight loss. He was a lifelong never-smoker and had no significant past medical history and no family history of malignancy.

After several recurrences of pneumonia, imaging studies ultimately thoracic lymphadenopathy, a mass right hilar mass, and a superior segment mass. He underwent a diagnostic CT guided biopsy and a staging PET/CT scan and was diagnosed with T4N2M0 (stage IIIb) adenocarcinoma of the lung. At the time of presentation, his WBC count was $12{,}000/mm^3$.

He started treatment with weekly carboplatin and paclitaxel for five weeks with concurrent intensity modulated radiotherapy (IMRT) to 50.4 Gy. During this treatment, his WBC count was $4300–10{,}700/mm^3$. A PET/CT scan 2 months after initiation of treatment demonstrated osseous progression. He then began treatment with cisplatin and pemetrexed. He tolerated this therapy well and had a normal WBC count (Figure 1, days 0–200). He subsequently started on pemetrexed maintenance therapy for 2 cycles. After cycle 2, he began noting right neck/supraclavicular swelling. A PET/CT scan demonstrated worsening of hypermetabolic soft tissue tumor burden, and elevated bone marrow fluorodeoxyglucose-avidity (FDG). Increased bone marrow FDG avidity can be seen in reactive marrow responding to chemotherapy, growth factor, or tumor infiltration along with other less likely processes. Additionally, his WBC count began rising (Figure 1, days 200–240). The leukocytosis primarily consisted of neutrophils, although there was a left-shift with some band neutrophils, metamyelocytes, myelocytes and promyelocytes present. He was initiated on a clinical trial of gemcitabine in combination with MLN8237, a second-generation Aurora A kinase inhibitor that is thought to act by inhibiting mitosis by acting on the

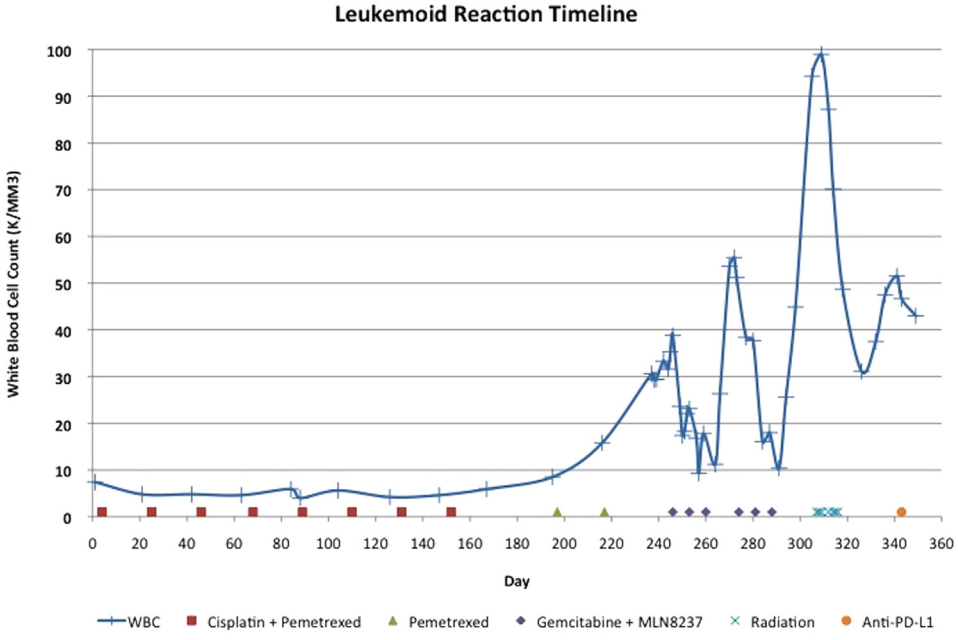

Figure 1 Correlation of WBC with anti-neoplastic therapy. WBC is expressed as $10^3/mm^3$. Anti-neoplastic treatments are also shown. Day number is from the time of diagnosis.